

# TRANSIENT RESPIRATORY SENSITIVITY TO SMALL MECHANICAL STIMULI ASSESSED BY SPONTANEOUSLY BREATHING ON A VENTILATOR

Lars Gösta Hellström<sup>1</sup> and Jan Persson<sup>2</sup>

<sup>1</sup> Division of Medical Engineering, Karolinska Institutet, Huddinge, Sweden

<sup>2</sup> Division of Anesthesiology and Intensive Care, Karolinska Institutet, Huddinge, Sweden

**Abstract** - Respiratory response to repeated sequences of mild negative inspiratory pressure (NIP) was investigated. Ten healthy male subjects were spontaneously breathing on a Siemens Servo Ventilator. The ventilator delivered the NIP loading (-2 cm H<sub>2</sub>O during 30 seconds at 1 min interval) and was also used as a measuring device. Six transient response sequences were ensemble-averaged to discern changes in the same order as normal variation of breathing at rest. Analysis of variance showed that NIP caused a moderate reduction in ventilation ( $V_I$ ), that was not compensated by increased respiratory activity ( $P_{0.1}$ ). The intra-individual coefficient of variation of these two breathing parameters decreased markedly ( $p < 0.05$ ), in a way that resembles restrictive lung disease. NIP loading might be an alternative test for clinical assessment of the lung and respiratory function. It is simple, and with repeated measurements, the sensitivity can be adjusted to interfere minimally with the patient.

**Keywords** - respiration, pressure load,  $P_{0.1}$ , sensitivity, variability

## I. INTRODUCTION

We have previously described how a commercial ventilator can be used for clinical studies of the respiratory function [1]. In contrast to ventilators with a built-in  $P_{0.1}$  facility [2], our method was specifically designed to retrieve continuous records of respiratory drive,  $P_{0.1}$  [3].

The respiratory function can be evaluated from the response to a stimulus (chemical or mechanical), most often hypercarbia or hypoxia. In a yet unpublished study we have investigated the respiratory response to carbon dioxide while breathing on a ventilator [4]. We examined a method with transient responses to intermittent small pulses of CO<sub>2</sub>. This approach reflects the ventilatory regulation closer to the control point [5] and being hardly noticeable, minimizes the risk of conscious influence on breathing in the awake patient.

Another way of achieving a stimulated breathing response is by applying mechanical provocations (pressure or resistance). The simplicity with which this can be accomplished while breathing on a ventilator was pointed out in our previous work, and was demonstrated at different negative and positive inspiratory pressures [1]. The interest of this work lies in the possibility of, in analogy with the CO<sub>2</sub> pulses above, studying the function of the respiratory centers by repeatedly evoking transient responses to small mechanical stimuli.

## II. METHODOLOGY

### A. Technique

A commercial ventilator (Servo Ventilator 900 C, Siemens-Elema, Stockholm) was used as a measuring device, using a technique previously described in detail elsewhere [1]. In brief, subjects wore nose-clips and were breathing spontaneously through a mouth-piece, attached to the ventilator via breathing hoses. Inspiratory flow, airway pressure and the pre-set negative inspiratory pressure (NIP, see below) level were acquired continuously from the ventilator by means of an attached Servo Computer Module, SCM 990 (Siemens-Elema, Stockholm), connected to the serial port of a personal computer. A standard humidifier (heat and moisture exchanger) was used. To improve the ventilator's servo control function, the airway pressure was measured at the "Y"-piece near the subjects airways instead of at the inspiratory and expiratory valves in the ventilator. Also connected to the same Y-piece was the sampling tube from a capnometer (Oscar Oxy, Datex, Helsinki).

Mechanical stimulation was applied by means of the PEEP (positive end expiratory pressure) control of this ventilator (working in the spontaneous breathing mode): when the PEEP is adjusted below zero, the Servo Ventilator creates negative inspiratory pressures (NIP), the expiratory pressure being unaffected.

### B. Subjects

Ten healthy male volunteers were studied, none with any known respiratory malfunction, all ignorant of the protocol and specific purpose of the study. They were instructed to concentrate on what they were listening to in their ear-phones and not to think about their breathing, even if the work of breathing varied. The subjects ages ranged 28-50 years, their weight 50-87 kg. They were asked to refrain from caffeine and nicotine three hours before the experiments. The experimental protocols were approved by the Ethical Committee of Karolinska Institutet.

### C. Procedures

The equipment was calibrated and adjusted before measurements. All subjects followed the same protocol. They were first introduced to the equipment. Then they were seated comfortably in an arm-chair, attached to the

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ventilator in the spontaneous breathing mode, and started listening to music or recorded short stories in ear phones, to come to rest. They adapted to quiet spontaneous breathing for at least five minutes.

After that six sequences with NIP pulses followed. The duration (30 seconds at 1 minute intervals), and the amplitude ( $-2 \text{ cm H}_2\text{O}$ ), of the pulses were controlled manually.

#### D. Calculations

A computer program was used to communicate with the Servo Computer Module (SCM), to read flow, pressure and NIP signals (22.5 seconds long data sequences at 66 Hz sampling frequency for each signal were continuously retrieved from the SCM). The program could also calculate ventilatory parameters, display results on the screen on a breath-by-breath basis, store results in a file and respond to user interaction from the keyboard. The parameters included inspiratory, expiratory and occlusion times, tidal and minute volume ( $V_I$ , tidal volume/breath time), respiratory drive ( $P_{0.1}$ ) and NIP level. End tidal carbon dioxide level ( $\text{ETCO}_2$ ) was not automatically recorded, but read manually at the end of each sequence.

For further analysis, data were imported to a spreadsheet program, designed with macro functions.

For the NIP pulses, the six 1 minute sequences were BIN-averaged, i.e. ensemble-averaged in 5 s bins, yielding one single representative response curve for each subject to analyze. The *normal* value of a parameter at rest was calculated as the mean value from the last 30 seconds “non-NIP” period. The *NIP* value was calculated as the mean value from the first 30 seconds NIP period. The *stimulated* value was calculated as the mean “induced” amplitude for a parameter, due to NIP stimulation (integral of the BIN-averaged response divided by the duration of a full sequence). The stimulated value represents the effective response level in a parameter, to be compared with the control level. The *baseline* was defined as the mean during the last minute before NIP pulses.

#### E. Statistical methods

The SPSS ver. 10.1 software was used to evaluate results. A generalized linear model of analysis of variance with repeated measures (GLM) was used to evaluate the influence of loads and pulse sequences, and a non-parametric Wilcoxon signed ranks test (NPAR) to compare various intervals.

### III. RESULTS

Recordings were very easily performed, and subjects cooperated without noticing the NIP pulses. Fig. 1 illustrates a recording for one subject (no 10), and how the influence of the mechanical loading is hidden by the natural variability of breathing.

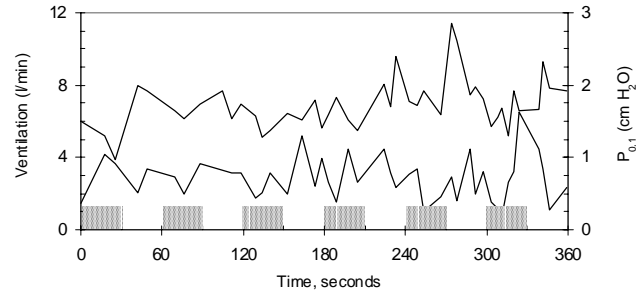


Fig. 1. Recording of the minute ventilation (upper) and the respiratory drive (lower) for one subject (no 10) during six NIP sequences (NIP indicated by shaded area). Note the variability of breathing at rest.

BIN-averaging the six NIP sequences resulted in the set of curves in fig. 2-3 for the ten subjects. The mean is represented by the thicker line. Results for the various intervals, together with coefficients of variation, are summarized in Table I.

Analysis of variance confirmed that  $V_I$  was reduced during NIP intervals (GLM,  $p < 0.001$ ), whereas differences in  $P_{0.1}$  were not significant between intervals. Similarly, stimulated value of  $V_I$  was significantly lower than normal (NPAR,  $p < 0.005$ ), whereas this was not the case for  $P_{0.1}$ .

The end tidal carbon dioxide level at the end of each pulse sequence did not differ from baseline.

The variability (intra-individual coefficient of variation) in  $V_I$  and  $P_{0.1}$  decreased significantly during NIP and non-NIP intervals in comparison with baseline (NPAR,  $p < 0.05$ ).

### IV. DISCUSSION

The reduction in minute ventilation would be expected. But it should be noted that the mechanical challenge of the small ( $-2 \text{ cm H}_2\text{O}$ ) NIP pulses, contrary to what might be expected, did not produce a measurable response in respiratory drive. As there was a clear response to  $-3 \text{ cm H}_2\text{O}$  NIP in our previous work [1], we conclude that there is a sensitivity threshold in the range  $-2$  to  $-3 \text{ cm H}_2\text{O}$  for NIP. The ventilator might influence this threshold, as breathing on a ventilator is a mechanical load *per se*, that normally induce an increased respiratory drive [1].

It cannot be ruled out that an increased number of NIP pulses, prolonged pulses, or a larger number of subjects, would lead to a significantly larger respiratory drive during

TABLE I

BREATHING RESPONSE TO PULSES OF NEGATIVE INSPIRATORY PRESSURE (NIP). PRESENTED AS MEAN AND STANDARD DEVIATION IN RESPECTIVE INTERVALS.					
	Ventilation	CV <sup>a</sup>	$P_{0.1}$	CV <sup>a</sup>	$\text{ETCO}_2$
Baseline	$9.28 \pm 1.50$	0.19	$1.06 \pm 1.31$	0.51	$5.21 \pm 0.43$
NIP	$8.30 \pm 1.11$	0.10	$1.14 \pm 0.49$	0.22	
Normal	$9.53 \pm 1.33$	0.12	$1.19 \pm 0.42$	0.23	$5.25 \pm 0.50$
Stimulated	$8.91 \pm 1.18$		$1.16 \pm 0.44$		

<sup>a</sup> Coefficient of variation

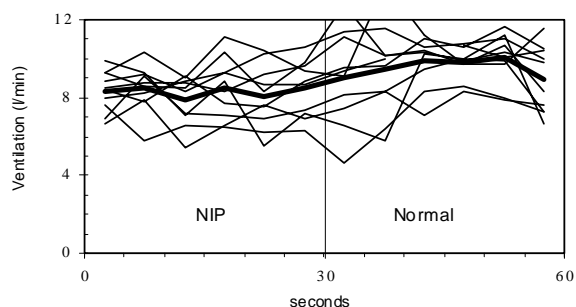


Fig. 2. BIN averaged response in minute ventilation ( $V_I$ ) for ten subjects. Negative inspiratory pressure (NIP) loading, followed by normal breathing.

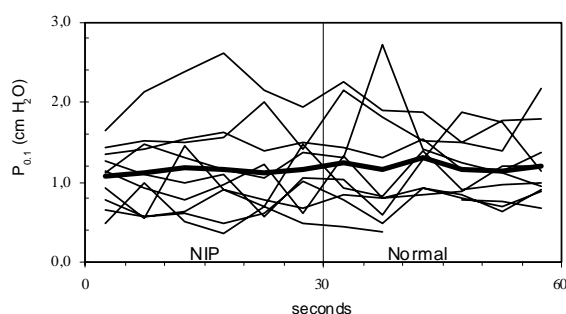


Fig. 3. BIN-averaged response in respiratory drive ( $P_{0.1}$ ) for ten subjects. Negative inspiratory pressure (NIP) loading, followed by normal breathing.

NIP sequences. It is a fact, though, that the end tidal  $\text{CO}_2$  level remained constant all through the measurements, indicating that there was some kind of compensation, possibly during the normal intervals (Threshold loads might take more than 30 seconds to be compensated for [6]), or due to a smaller relative dead-space. Again, this was not statistically confirmed from this study.

The stimulated level is an estimate of the change from control level, that resulted from the loading. The stimulated  $V_I$  was only -6 % from control in this case, and the stimulated  $P_{0.1}$  -2 %. This is in the range of normal pressure variations in thorax. It would probably be better to choose a level of loading that yields responses twice as large. Such a level of loading would probably still supply a “non-interfering” mechanical challenge.

The decreased variability of the breathing during the NIP sequences is an interesting finding. The normal variation of respiratory parameters is well known [1, 7, 8], and our results at baseline fits very well into this picture. But the narrowing of the coefficient of variation (CV) during the NIP sequences is remarkable. It has been shown that patients with restrictive lung disease, such as pulmonary tuberculosis or pneumonitis, has smaller CV than normal subjects, whereas patients with obstructive lung disease, as emphysema or bronchial asthma, has significantly greater CV [9]. But we cannot see that CV narrowing from pressure loading has been reported before. Our interpretation is that this is a natural response to NIP. The experience of an increased work of breathing from the pressure loading may

simulate the stiffness of restrictive lungs. Contrary to a resistive load, which adds resistance to breathing, pressure loads has the effect of reducing compliance (mathematically, this is expressed by a smaller  $dV/dP$  with NIP).

There follows an interesting possibility with NIP loading: Increased lung dysfunction can temporarily be simulated in a patient. For example, what would be the effect of increased obesity (a very frequent restriction to breathing) in the obstructive lung patient?

Another possibility with NIP could be as a training tool, to stimulate the respiratory muscles of a patient with a neuro-muscular disease.

$P_{0.1}$  is often proposed as an indicator of weaning success from a ventilator [10, 11]. A high value indicates increased neuro-muscular activity, and an increased risk for muscle fatigue. Similarly,  $P_{0.1}$  can be used to estimate a suitable level for pressure support ventilation (PSV) [12]. We suggest that a NIP challenge would presumably give added information on the residual potential of the respiratory function. A weak response would indicate a risk.

A better assessment of lung function in the ventilated patient is sometimes sought after, see for instance [13, 14]. Simple mechanical challenges could perhaps improve the evaluation of severity in some diseases, for instance sleep disorders [15, 16], pulmonary disease [17] and neuro-muscular disease [18].

Major features of NIP versus  $\text{CO}_2$  loading is that it is simple and fast, but also that it differs qualitatively, in affecting other physiological mechanisms in the respiratory regulation. That has partly been addressed in this report. We would suggest that a mechanical sensitivity test should be considered in patients with a suspected reduced neuromuscular activity or abnormal lung mechanics.

## V. CONCLUSIONS

Respiratory sensitivity can be measured using a method with repeated small negative inspiratory pressure pulses. It is simple, interferes minimally with the patient, and is sensitive to changes hidden by normal variability in breathing. It can be used for clinical assessment of the lung and respiratory function. Specifically, it may be used to simulate restrictive lung disease. For any application, an appropriate level and duration of the stimulus, has to be found, preferably greater than was used in this study.

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